Remarks

Claim Objections. Claims 1 and 12 are objected to because of the following informalities. In Claim 1, last 2 lines, the term "amides" is listed twice for the description of the "L group". This occurrence is also set forth in Claim 12, lines 9 and 11. In response to these objections, Applicant respectfully submits claims to her invention that have been amended to delete the duplicate terms in Claims 1 and 12.

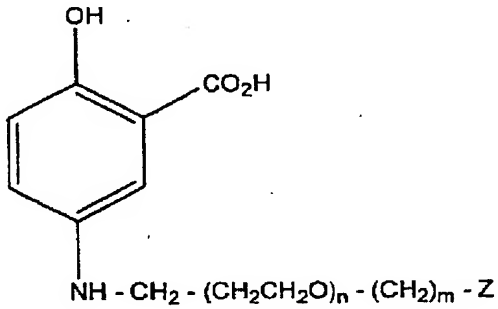
Rejections Under 35 USC §112. (Sections numbered 1 and 2 of the Office Action) Claims 1-5, 7, 9, 10 and 12-18 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 1, 2, 10 and 13-16, the metes and bounds of the term "sugar residue" cannot be determined which renders the claims indefinite. Likewise, the term "sugar residue" in dependent Claims 3-5 should be changed in order to comply with proper antecedent basis. In addition, in Claims 1, 9, and 12-16, the "Z" symbol is described by properties. This functional description makes it difficult to determine the identity of the Z moiety, which renders Claims 1, 9, and 12-16 vague and indefinite. Further, Claim 10 stands rejected, since the claim recites a process step that involves alkylating the amino group of 5-aminosalicylic acid with a reducing sugar. However, the term "alkylating" refers to the substitution of an alkyl group for hydrogen atom in a cyclic compound. There is no indication in the instantly claimed procedure that an alkyl group is being substituted since the reactants are a sugar and an amino group. Likewise, Claims 14 and 15 stand rejected, since the metes and bounds of the text "prophylactically or interventionally treating a potential or developed condition or disease state in a human or non-human mammalian subject" cannot be determined which renders the claims indefinite. Similarly, Claims 17 and 18 stand rejected, since the metes and bounds of the term "5-amino acid derivative" cannot be determined since Claims 17 and 18 do not clarify or give a

detail description of the term "5-amino acid derivative". Claims 7 and 9 also stand rejected, since these claims are dependent upon Claim 1 and do not clarify the error disclosed for the above rejection of Claim 1.

Claims 1, 2, 10 and 13-16 stand rejected, since the metes and bounds of the term "sugar residue" cannot be determined which renders the claims indefinite. In Claims 1, 2, 10 and 13-16, as the Examiner suggested, Applicant has amended the claims to replace the term "sugar residue" with the word "sugar." The term "sugar residue" has also been changed in Claims 3-5 in order to comply with proper antecedent basis. In support of the proposed amendment, Applicant respectfully submits that in the Specification for the present invention, she discloses that in this embodiment of her present invention, the substituent on the nitrogen of the amino group of 5-aminosalicylic acid is a sugar in which a covalent bond to the oxygen of a hydroxyl group originally substituted on the parent sugar compound has been replaced by a covalent bond to the nitrogen of the amino group of 5-aminosalicylic acid (page10, lines 16-19).

Likewise, Claims 1, 9, and 12-16 stand rejected, since in these Claims the "Z" symbol is described by properties. The Examiner has stated that this functional description makes it difficult to determine the identity of the Z moiety, which renders Claims 1, 9, and 12-16 vague and indefinite. So as to more adequately disclose her invention and more clearly define the identity of the Z moiety, Applicant has amended Claims 1, 9, and 12-16 to identify the Z moiety as a drug or therapeutic agent that is covalently joined to the terminus of a poly(ethylene glycol) chain-containing tether that is distal to the terminus of the poly(ethylene glycol) chain-containing tether that is joined to the nitrogen of the amino group of 5-aminosalicylic acid. Applicant submits that the Specification of her present invention discloses on page 8, lines 14-22, that by the term "drug" is meant any pharmaceutical or physiological agent, composition, bioactive compound, or combination thereof, useful in the diagnosis, cure, mitigation, treatment, or

prevention of a disease, or for any other medical or veterinary purpose. The term "drug" is intended to be interpreted broadly and is not limited in terms of chemical composition or biological activity. Likewise, the Specification discloses that by the term "therapeutic agent" is meant an agent which is therapeutically useful, e.g., an agent for the prevention, treatment, remission or attenuation of a disease state, physiological condition, symptoms, or etiological factors, or for the evaluation or diagnosis thereof. Restated for clarity, this embodiment of Applicant's present invention specifically comprises a poly(ethylene glycol)-chain containing tether having the general formula:



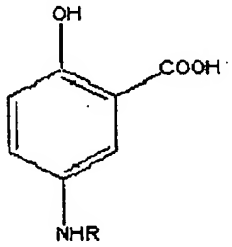
wherein one terminus of the poly(ethylene glycol) chain-containing tether is covalently joined to the nitrogen atom of the amino group of 5-aminosalicylic acid, n is a positive integer from one to about 100, m is 2, 3, or 4, and Z is a drug or therapeutic agent that is covalently joined to the other terminus of the poly(ethylene glycol) chain-containing tether. Further, Applicant respectfully submits that in the Specification for her present invention she discloses significant advantages attendant to this embodiment of her present invention, wherein the therapeutic benefits of both 5-aminosalicylic acid and the (second) drug covalently tethered thereto by the PEG segment are delivered therapeutically to the subject (page 14, lines 24-26, and pages 15 and 16, lines 12-26 and lines 1-8, respectively). In addition, in the Specification for her present invention, she discloses non-limiting examples of this embodiment of her present invention,

including examples in which the drug or therapeutic agent is lipoic acid (pages 15 and 16, lines 12-26 and lines 1-8, respectively, and Example 5), an immunomodulator, an antibacterial, or an antioxidant (page 10, lines 5 and 6).

Claim 10 stands rejected, since the claim recites a process step that involves alkylating the amino group of 5-aminosalicylic acid with a reducing sugar. However, the term "alkylating" refers to the substitution of an alkyl group for hydrogen atom in a cyclic compound. There is no indication in the instantly claimed procedure that an alkyl group is being substituted since the reactants are a sugar and an amino group. Applicant has amended Claim 10 to recite a process step that involves reacting the amino group of 5-aminosalicylic acid with a reducing sugar. Applicant's Specification discloses an example of a process of Claim 10 in Example 1, in which D-(+)-glucose is reacted with 5-aminosalicylic acid in methanol/water solution containing 1.1 mole equivalents of triethylamine, and in Example 3, where the preparation of other, heretofore unknown glycoconjugates of 5-aminosalicylic acid is disclosed by Applicant.

Likewise, Claims 14 and 15 stand rejected, since the metes and bounds of the text "prophylactically or interventionally treating a potential or developed condition or disease state in a human or non-human mammalian subject" cannot be determined which renders the claims indefinite. Applicant has amended Claims 14 and 15 to define the metes and bounds of her present invention and claim a method of prophylactically or interventionally treating an inflammatory disease in the gastrointestinal tract of a human or non-human mammalian subject. In support of amendment, Applicant respectfully submits that Examples 7 and 8 of the Specification disclosing her present invention, for example, disclose that therapeutic 5-aminosalicylic acid compositions of her invention are useful for the treatment of inflammatory bowel disease, a spectrum of chronic, idiopathic inflammatory disorders of the gastrointestinal tract that include Crohn's disease and ulcerative colitis.

Similarly, Claims 17 and 18 stand rejected, since the metes and bounds of the term "5-amino acid derivative" cannot be determined since Claims 17 and 18 do not clarify or give a detail description of the term "5-amino acid derivative". Applicant has amended Claims 17 and 18 to more adequately disclose the metes and bounds of the term "5-aminosalicylic acid derivative composition" by specifying a 5-aminosalicylic acid derivative composition having the general formula:



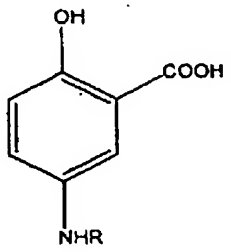
wherein R is a sugar, with the exception that the sugar is not D-glucose; a poly(ethylene glycol) chain-containing residue having the general formula $-CH_2CH_2CH_2-(CH_2CH_2O)_n-R_1$, R_1 is H or a linear or branched lower alkyl group having from one to about 6 carbons, and n is a positive integer from about 3 to about 100; or a poly(ethylene glycol) chain-containing tether having the general formula $-CH_2-(CH_2CH_2O)_n-(CH_2)_m-Z$, in which n is a positive integer from about 3 to about 100, m is 2, 3, or 4, and Z is a drug or therapeutic agent selected from the group consisting of lipoic acid, immunomodulators, antibacterials, and antioxidants that is covalently joined to the distal terminus of said poly(ethylene glycol) chain-containing tether. Applicant discloses these embodiments of her present invention in the Specification, for example, on pages 9 and 10, beginning on line 19 of page 9 for clarity and continuing through line 6 on page 10, as well as pages 14-16, beginning with line 24 on page 14 and ending on line 8 on page 16.

Rejections Under 35 U.S.C. 102(b). (Sections 4 and 5 of the Office Action) Claims 1-3, 5, 6, 13, 17 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tjoernelund *et al.*

(*Journal of Chromatography*, "Stability of 5-Aminosalicylic Acid and Its Metabolites in Plasma at -20°C: Formation of N-β-D-Glucopyranosyl-5-Aminosalicylic Acid," 1991, Vol. 570, No. 1, 224-228). The Tjoernelund *et al.* reference (*Xenobiotica*, "New Metabolites of the Drug 5-Aminosalicylic Acid I: N-β-D-Glucopyranosyl-5-Aminosalicylic Acid", 1989, Vol. 19, No. 8, pp. 891-899), which also discloses N-β-D-glucopyranosyl-5-aminosalicylic acid, has been cited both by Applicant and the Examiner.

Applicant respectfully traverses the Examiner's rejection under U.S.C. 102(b) that her claimed invention is anticipated by Tjoernelund *et al.* In the Tjoernelund *et al.* reference (*Xenobiotica*, "New Metabolites of the Drug 5-Aminosalicylic Acid I: N-β-D-Glucopyranosyl-5-Aminosalicylic Acid", 1989, Vol. 19, No. 8, pp. 891-899), Tjoernelund *et al.* reported that a metabolite of 5-aminosalicylic acid, N-β-D-glucopyranosyl-5-aminosalicylic acid, was detected during HPLC analysis of plasma samples from human volunteers who had been dosed intravenously with 5-aminosalicylic acid, during HPLC analysis of samples obtained by incubation of 5-aminosalicylic acid with rat liver homogenate, or during HPLC analysis of samples obtained by reaction of 5-aminosalicylic acid and glucose in phosphate buffer, pH 7.4. In the reports of Tjoernelund *et al.* in *Xenobiotica*, Vol. 19, pp 891-899, 1989, and the *Journal of Chromatography*, Vol. 270, pp 224-228, 1991, the authors found that N-β-D-glucopyranosyl-5-aminosalicylic acid was obtained transiently by and was an unstable and impure product of reaction of 5-aminosalicylic acid with glucose under these specific conditions. Tjoernelund *et al.* reported that N-β-D-glucopyranosyl-5-aminosalicylic acid was "unstable and decomposed" during determination of the nmr spectrum (page 893 of the *Xenobiotica* report), over time as short as a few hours (Figure 5, page 896 of the *Xenobiotica* report), upon thawing of plasma samples containing the compound, or after the addition of 0.2 M potassium phosphate buffer, pH 3.0 (page 225 of the *Journal of Chromatography* report).

In contrast to the reports of Tjoernelund *et al.*, Applicant has unexpectedly discovered that glycosylated derivatives of 5-aminosalicylic acid having the general formula:

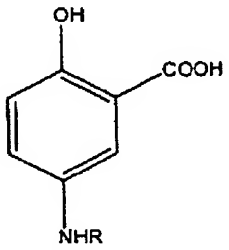


wherein R is a sugar, are obtained as stable products of the reaction of a reducing sugar with 5-aminosalicylic acid in water/alcohol solution. By way of example of her unexpected discovery, Applicant discloses that N-β-D-glucopyranosyl-5-aminosalicylic acid is prepared as a stable product of the reaction of glucose and 5-aminosalicylic acid in methanol/water solution containing triethylamine. Applicant's discovery differs significantly from the reports of Tjoernelund *et al.* For example, Applicant uses a water/alcohol solution (Example 1 of the Specification for the present invention) as the reaction medium, whereas Tojernelund *et al.* identified N-β-D-glucopyranosyl-5-aminosalicylic acid as an unstable product from some unspecified reaction of 5-aminosalicylic acid with glucose in human plasma or in rat liver homogenates, or from reaction in phosphate buffer, pH 7.4. Further, Applicant obtains pure products of her invention, and the products of her invention are stable. In contrast, Tjoernelund *et al.* reported product mixtures containing an unstable product identified as N-β-D-glucopyranosyl-5-aminosalicylic acid as well as other unidentified compounds, mixtures in which the presumed N-β-D-glucopyranosyl-5-aminosalicylic acid decomposed during determination of the nmr spectrum (page 893 of the *Xenobiotica* report), over time as short as a few hours (Figure 5, page 896 of the *Xenobiotica* report), upon thawing of plasma samples containing the compound, or after the addition of 0.2 M potassium phosphate buffer, pH 3.0 (page 225 of the *Journal of Chromatography* report).

Notwithstanding these differences in the teachings of Tjoernelund *et al.*, Applicant respectfully submits that the references fall far short of contemplating or suggesting Applicant's claimed invention. Applicant has unexpectedly discovered that covalent bonding between the nitrogen of the amino group of 5-aminosalicylic acid and a sugar; a poly(ethylene glycol) chain-containing residue having the general formula $-CH_2CH_2CH_2-(CH_2CH_2O)_n-R_1$, wherein R_1 is H or a linear or branched lower alkyl group having from one to about 6 carbons, and n is a positive integer from about 3 to about 100; or a poly(ethylene glycol) chain-containing tether having the general formula $-CH_2-(CH_2CH_2O)_n-(CH_2)_m-Z$, in which n is a positive integer from about 3 to about 100, m is 2, 3, or 4, and Z is a drug or therapeutic agent that is covalently joined to the distal terminus of said poly(ethylene glycol) chain-containing tether, beneficially and unexpectedly alters the physico-chemical and biological properties of the heretofore unknown therapeutic 5-aminosalicylic acid derivatives to enhance retention in the gastrointestinal tract and decrease the transfer of the derivatives from the lumen of the gastrointestinal tract to the systemic circulation; to show activity in the prophylaxis or treatment of inflammatory conditions or disease states in a mammalian subject or a cell or tissue therefrom, particularly inflammatory conditions of the bowel; and to enhance *in vivo* resistance to enzymatic degradation, relative to 5-aminosalicylic acid alone. In contrast, the Tjoernelund *et al.* reports consist merely in the identification of N-β-D-glucopyranosyl-5-aminosalicylic acid by HPLC, nmr, and mass spectrum as an unstable product of the reaction of 5-aminosalicylic acid and D-glucose in human plasma or rat liver homogenates, or in phosphate buffer, pH 7.4. The Tjoernelund *et al.* reports present no data and completely lack statements that contemplate or suggest obtaining other glycoconjugates of 5-aminosalicylic acid by reacting 5-aminosalicylic acid with other monosaccharides, disaccharides, or polysaccharides, as disclosed by Applicant, nor do Tjoernelund *et al.* contemplate or suggest reaction conditions under which said glycoconjugates could be obtained as stable products. Further, Tjoernelund *et al.* do not contemplate or suggest therapeutic activity of the N-β-D-glucopyranosyl-5-aminosalicylic acid, its topical application in

lieu of and as a source of 5-aminosalicylic acid for the treatment of inflammatory conditions or disease states, an enhancement of retention of this 5-aminosalicylic acid derivative in the gastrointestinal tract of a subject, an enhanced *in vivo* resistance of this 5-aminosalicylic acid derivative to enzymatic degradation, relative to 5-aminosalicylic acid alone, or delivery to mammals in pharmaceutical dosage forms containing this 5-aminosalicylic acid derivative, said pharmaceutical dosage forms being useful for the prevention or treatment of inflammatory diseases, in particular inflammatory diseases of the gastrointestinal tract or bowel.

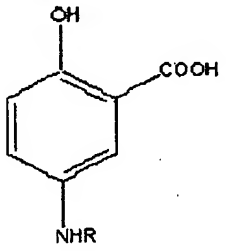
Applicant respectfully submits two additional independent claims, numbered 19 and 20. Claim 19 is an independent claim that comprises a physiologically active therapeutic 5-aminosalicylic acid derivative composition having the general formula:



wherein R is a deoxysugar, with the exception that the deoxysugar is not 1-deoxyglucose; a poly(ethylene glycol) chain-containing residue having the general formula $-CH_2CH_2CH_2-(CH_2CH_2O)_n-R_1$, R_1 is H or a linear or branched lower alkyl group having from one to about 6 carbons, and n is a positive integer from about 3 to about 100; or a poly(ethylene glycol) chain-containing tether having the general formula $-CH_2-(CH_2CH_2O)_n-(CH_2)_m-Z$, in which n is a positive integer from about 3 to about 100, m is 2, 3, or 4, and Z is a drug or therapeutic agent selected from the group consisting of lipoic acid, immunomodulators, antibacterials, and antioxidants that is covalently joined to the distal terminus of said poly(ethylene glycol) chain-containing tether, wherein the derivative composition is active in the prophylaxis or treatment of

inflammatory conditions or disease states in a mammalian subject or a cell or tissue therefrom. Claim 20 is an independent claim that comprises a method of stabilizingly and structurally modifying 5-aminosalicylic acid in a manner that enhances its retention in the gastrointestinal tract and decreases the transfer of said acid from the lumen of the gastrointestinal tract to the systemic circulation comprising covalently conjugating the nitrogen atom of the amino group of 5-aminosalicylic acid to a 1-deoxy sugar; a poly(ethylene glycol)-containing residue having the general formula $-CH_2CH_2CH_2-(CH_2CH_2O)_n-R_1$, wherein R_1 is H or a linear or branched lower alkyl group having from one to about 6 carbons, and n is a positive integer from about 3 to about 100; or a poly(ethylene glycol) chain-containing tether having the general formula $-CH_2-(CH_2CH_2O)_n-(CH_2)_m-Z$, in which n is a positive integer from about 3 to about 100, m is 2, 3, or 4, and Z is a drug or therapeutic agent selected from the group consisting of lipoic acid, immunomodulators, antibacterials, and antioxidants that is covalently joined to the distal terminus of said poly(ethylene glycol) chain-containing tether. Applicant respectfully submits that both new claims are directed to aspects of the invention for which search has likely been completed by the Examiner.

In her present invention Applicant discloses her surprising discovery of novel, therapeutic 5-aminosalicylic acid derivative compositions having the general formula



wherein R is a sugar, a poly(ethylene glycol)-containing residue, or a poly(ethylene glycol) chain-containing tether joining the amino group of 5-aminosalicylic acid at one terminus of the tether and a drug or therapeutic agent at the other terminus of the tether. Further, Applicant has

unexpectedly discovered a novel method of delivery of 5-aminosalicylic acid to the gastrointestinal tract following oral administration of said 5-aminosalicylic acid derivative compositions in pharmaceutical preparations and to pharmaceutical compositions containing the therapeutic 5-aminosalicylic acid derivative compositions of her present invention. Likewise, Applicant has unexpectedly discovered that the therapeutic 5-aminosalicylic acid derivative compositions of her invention are stabilized in a manner that will enhance the retention of said compositions in the intestine, decrease the cellular absorption thereof, and decrease the transfer of said compositions or the 5-aminosalicylic acid derived therefrom to the systemic circulation. Her invention is based upon her unexpected discovery that the topical delivery of therapeutically effective amounts of therapeutic 5-aminosalicylic acid derivative compositions of her invention to the gastrointestinal tract following oral administration in a pharmaceutically acceptable dosage form enables significant advances in the medical arts, particularly in the treatment of inflammatory bowel diseases.

In view of the foregoing, Applicant respectfully submits that the claims to her invention, as amended, are in condition for allowance and respectfully requests reconsideration thereof.

Should additional information be required, Deanna J. Nelson is representing Applicant before the Office. She is available by telephone at (919) 678-9478 during the hours of 8:00 AM to 4:00 PM Monday through Friday and by facsimile at (919) 678-9474.

Respectfully submitted,

Deanna J. Nelson

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